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| APPLICATION NO.   | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 10/556,231  | 11/08/2005  | Susumu Nishiguchi    | 18900-003US1        | 3664             |
| 26211   | 7590        | 06/09/2009           | EXAMINER            |                  |
| FISH & RICHARDSON P.C.<br>P.O. BOX 1022<br>MINNEAPOLIS, MN 55440-1022 |             |                      | NGUYEN, VU ANH      |                  |
|   |             |                      | ART UNIT            | PAPER NUMBER     |
|   |             |                      | 1796                |                  |
|   |             |                      | NOTIFICATION DATE   | DELIVERY MODE    |
|   |             |                      | 06/09/2009          | ELECTRONIC       |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/556,231             | NISHIGUCHI ET AL.   |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | Vu Nguyen              | 1796                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 29 April 2009.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-4, 8, 9, 12-15, 20, 25 and 26 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-4, 8, 9, 12-15, 20, 25 and 26 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/SB/08)  
 Paper No(s)/Mail Date \_\_\_\_\_.  
 4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date \_\_\_\_\_.  
 5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_.

## DETAILED ACTION

### ***Response to Amendment***

1. This Office action is in response to the Amendment filed 04/29/2009. The title and claims 1-3, 5, 8, 10, 20, 25 and 26 have been amended. Claims 5-7, 10, 11, 16-19 and 21-24 remain withdrawn as directed to non-elected species. Claims 1-4, 8, 9, 12-15, 20, 25 and 26 are pending in this application.

### ***Claim Rejections - 35 USC § 103***

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. Claims 1-3, 8, 9, 13, 14, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nishiguchi et al. (US 6,046,040) in view of Huang et al. (Adv. Synth.

Catal. 343 (6-7), 2001, 675-681) with evidentiary support from Ni et al. (Chinese Chemical Letters, 18 (2007), 79-80).

5. Regarding the limitations set forth in these claims, Nishiguchi et al. (Nishiguchi, hereafter) teaches a water-soluble polymer compound similar to the compound recited in claims 1 and 8-9 except for the content of the (meth)acrylic acid residue (see, for example, the species in reference example 13 in col. 23). The polymer to which the sugar-containing amino acid residue is attached to via a linker comprises any polymer or copolymer that is soluble in aqueous media (col. 6-7, bridging paragraph) and includes copolymers of (meth)acrylic acid, (meth)acrylamide, and other vinyl monomers. The linker is attached to the water-soluble polymer via the acrylamide repeating units, not acrylic acid repeating units (col. 10; col. 18, reference example 5; col. 19-20, 1<sup>st</sup> and 3<sup>rd</sup> formulae; col. 21-22, 2<sup>nd</sup> formula; col. 23-28). Corresponding to claims 13-14, the disclosed compound has cleavable linkage in the linker that can be cleaved by  $\alpha$ -chymotrypsin or ceramide glycanase (col. 7, lines 15-33). The compound is used as a primer in glycoconjugate synthesis.

6. Clearly, Nishiguchi teaches all the limitations set forth in these claims but fails to specify a content of (meth)acrylic acid in the water-soluble copolymers.

7. Huang et al. (Huang, hereafter) teaches homogeneous enzymatic synthesis using a thermo-responsive water-soluble polymer support. The study is particularly directed to enzymatic glycosylation using a primer having a mono- or oligo-saccharide residue attached to a thermo-responsive polymer via a linker (Scheme 1 on page 677). The thermo-responsive polymer comprises N-isopropylacrylamide, acrylic acid, with or

without N-tert-butylacrylamide (Figure 1 on page 676). Depending on the proportions of the monomers, the thermo-responsive polymers possess different lower critical solution temperatures (LCST). All things being equal, an increase in the content of acrylic acid in a copolymer tends to increase the LCST of the copolymer as shown in polymers A and B (Figure 1, page 676). The study is an attempt to correlate the LCST of the thermo-responsive polymer with (1) the efficiency of the enzymatic synthesis, (2) the ease of product separation and purification, and (3) the recyclability of the catalytic system.

**[Motivations]** Accordingly, the followings are taught: (A) if the polymer is not soluble during the glycosylation, potential complications such as low reactivity, non-linear kinetics, stereochemical complexity, and analytical difficulty tend to occur (Introduction); (B) if the polymer is soluble during the glycosylation, the composition of the polymer can be manipulated to change its LCST so as to (a) increase the efficiency of the glycosylation and (b) enable facile isolation of the products as well as facilitate the recyclability of the catalytic system (p. 676).

8. It is well known in the art that in a thermo-responsive copolymer such as random copolymer of N-isopropylacrylamide (NIPAM) and acrylic acid (AA), increasing the content of the acrylic acid will increase the LCST of the copolymer. (See Ni, Figure 1). Thus, if an intended enzymatic reaction is done at, say 35°C, a copolymer of NIPAM and AA having about 10 mol% of AA would have LCST lower than 35°C (i.e., it is insoluble at that temperature) and it is therefore not beneficial to the reaction.

9. From the teachings of Huang and considering that Nishiguchi needs a polymer that is soluble during the enzymatic reaction, and since the temperature at which sugar-

transfer enzymes are active includes temperatures greater than 37°C, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to have modified the compound taught by Nishiguchi by employing, as support polymer, copolymers of acrylic acid and acrylamide derivatives having different contents of acrylic acid so that the copolymers have different LCST's and are suitable for a wide range of glycosyltransferases-catalyzed reactions. That is, one of ordinary skill in the art would realize from the teachings of Huang that, when the activity of an enzyme is such that the reaction is best carried out at a relatively high temperature, a support polymer having a high content of acrylic acid (i.e., having a high LCST) is more suitable since it is more likely to be soluble in the reaction medium at the reaction temperature, and since the reaction product can be easily isolated by precipitating the polymer with a temperature above its LCST.

10. Claims 1-3, 12-15, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nishiguchi et al. (JP 2001-220399 A) in view of Huang et al. (Adv. Synth. Catal. 343 (6-7), 2001, 675-681) with evidentiary support from Ni et al. (Chinese Chemical Letters, 18 (2007), 79-80).

11. Regarding the limitations set forth in these claims, Nishiguchi et al. ('399, hereafter) teaches a polymer carrier having monosaccharide residues connected to protease-uncleavable peptide residues (A), which are connected to protease-cleavable amino acid residues or peptide residues (B), which are attached to a polymer (D) via a linker (C), which has 1-20 methylene units (Claim 1). The peptide (A) comprises 2-30

amino acids (Claim 2). The polymer (D) comprises copolymers of vinyl compounds such as (meth)acrylamides, (meth)acrylic acids, styrene, and fatty acid vinyl ester (Claim 6). The linker (C) is bonded to the polymer (D) via acrylamide repeating units (Claim 8). The polymer carrier is used for glycoconjugate synthesis (Claims 13-16). The resulting glycoconjugate can be released from the carrier polymer by cleaving a linkage in (B) with a specific protease or by hydrolysis with  $\alpha$ -chymotrypsin (Claims 19-20). The polymer (D) is preferably water-soluble [0031].

12. Clearly, '399 teaches all the limitations set forth in these claims but fails to specify a content of (meth)acrylic acid in the water-soluble copolymers.

13. Huang teaches homogeneous enzymatic synthesis using a thermo-responsive water-soluble polymer support as discussed above. For the reasons set forth in paragraphs 7-9 above, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to have modified the polymer carrier taught by '399 by employing, as support polymer, copolymers of acrylic acid and acrylamide derivatives having different contents of acrylic acid so that the copolymers have different LCST's and are suitable for a wide range of glycosyltransferases-catalyzed reactions.

14. Claims 1-4, 8-9, 13-14, 20, 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamada et al. (Carbohydrate Research 305 (1998), 443-461) in view of Huang et al. (Adv. Synth. Catal. 343 (6-7), 2001, 675-681) with evidential support from Dalkas et al. (Polymer 47 (2006) 243-248).

15. Regarding the limitations set forth in these claims, Yamada et al. (Yamada, hereafter) teaches high performance polymer supports (primers) for enzyme-assisted synthesis of glycoconjugates and a method of preparation thereof. Except for an absence of (meth)acrylic acid, the disclosed supports and the disclosed method are similar to the claimed compound and the claimed method (Figure 1; Schemes 1-3). The resulting glycoconjugate is released from the support by cleaving the linker by hydrogenolysis, hydrolysis with  $\alpha$ -chymotrypsin, or transglycosylation using ceramide glycanase (Abstract). The supports of the primers comprise water-soluble polyacrylamide copolymer (Scheme 3, compound 20). The followings are noted: monomer (3) (Figure 1) corresponds to the compound in claims 8-9, and monomer (1) (Figure 1) corresponds to the monomer of claims 21-23. The methods of claims 25 and 26 are taught using hydrogen-sensitive primer (i.e., cleavable by hydrogenolysis),  $\alpha$ -chymotrypsin-sensitive primer (i.e., cleavable by  $\alpha$ -chymotrypsin), and primer cleavable by ceramide glycanase (page 444, right column; page 446; page 451, section C). It is also disclosed that “enzymatic extension of the carbohydrate chains on water-soluble polymer with flexible anchors has advantages of facilitating efficient separation of the products from the reactants, and permitting high reactivity” (p. 444, section 2, 3<sup>rd</sup> sentence).

16. Clearly, Yamada teaches all the limitations set forth in these claims but fails to teach a support polymer having the recited content of (meth)acrylic acid.

17. Huang teaches homogeneous enzymatic synthesis using a thermo-responsive water-soluble polymer support as discussed in paragraph 7 above. It is to be reiterated

that Huang is directed to carrier polymers having different LCST so that, for a selected glycoconjugate synthesis using a specific glycosyltransferase, an appropriate carrier polymer can be selected such that the whole primer is soluble at the reaction temperature and the final product can be isolated easily by increasing the temperature above the LCST (and thereby precipitating the primer). The polymer is based on NIPAM and the LCST is changed by incorporating different content of acrylic acid and N-tert-butylacrylamide.

18. It is well known in the art that, unlike homopolymer of NIPAM, homopolymer of acrylamide is not thermo-responsive and is highly soluble in water (Dalkas et al. page 244, section 3.1). Accordingly, one skilled in the art would realize that the primer taught by Yamada has an important drawback in that, even though the primer is designed to facilitate “efficient separation of the products from the reactants,” the use of only acrylamide does not work toward that end since the separation can not be achieved simply by changing the temperature to precipitate either the products or the reactants.

19. In light of the teachings by Huang, it would have been obvious to a person having ordinary skill in the art at the time the invention was made to have modified the polymer supports taught by Yamada by employing copolymers of NIPAM and AA having different contents of AA so that the primers are soluble at the reaction temperatures (i.e., the efficiency of the corresponding glycoconjugate synthesis is enhanced) and the separation of the products from the reactants can be carried out simply by increasing the temperature above the LCST of said support polymer to precipitate the primer. Since some of the glycoconjugate synthesis reactions taught by Yamada are done at

37°C (p. 455, 1<sup>st</sup> section), one skilled the art would be motivated to prepare and use NIPAM-AA copolymers having greater than 20 mol% of AA since these polymers are more likely to have LCST greater than 37°C.

### ***Response to Arguments***

2. Applicant's arguments filed 04/29/2009 have been fully considered but they are not persuasive. Specifically, the applicant alleges that (1) Huang does not teach a polymer containing acrylic acid (p. 10, next-to-last paragraph), (2) Huang discusses the effect of LCST on enzyme activity of enzyme-polymer adduct, not on activity of a primer (p. 11, first paragraph), and (3) the data provided by Dai contradicts the examiner's assertion on the relationship of LCST and the amount of acrylic acid in a thermo-responsive polymer (pages 11-12, bridging paragraph).

3. Dai is no longer employed as evidentiary support in the rejections and, accordingly, applicant's argument relating to the Dai reference is moot.

4. In response to allegations (1) and (2), Huang does teach a polymer containing acrylic acid (see structure 7 on page 677) and it does teach the effect of LCST on the activity of a primer (pages 677-678). The NASI units in the polymers in Figure 1 (p. 676) are converted to acrylic acid units as shown in the steps of making the structure 7 on page 677. The effects of the LCST of the polymer which is part of a primer construction are also discussed. Thus, "we present our studies of enzymes attached to such polymers as recyclable biocatalysts and enzymatic carbohydrate synthesis with **glycosyl acceptors immobilized on the polymer through a cleavable linker**. Due to

the high solubility of oligosaccharides in water and the high cost of enzymes, it is desirable to carry out enzymatic synthesis in such systems, which would **allow the recovery of enzymes and products by gentle heating after the reaction.**" (p. 675).

An example of subjecting the primer 7 to a galactosylation reaction followed by precipitating the polymer by heating to 55°C is also given (p. 678, left column).

5. The examiner has provided ample reasons to show the followings. First, the optimum temperature for certain enzyme-catalyzed reactions is higher than ambient temperature. Second, according to Huang, a polymer, whether in context of being an enzyme support or a primer carrier, should be in soluble form at the reaction temperature (for optimum reaction yield) and should be in insoluble form upon further heating (for ease of product recovery). Third, in such polymer, increasing the content of acrylic acid will increase the LCST. Such effect of acrylic acid on the LCST of a thermo-responsive copolymer is well known in the art, such as in Huang (Table in Figure 1, Polymers A and B), and in Ni (above). Forth, it would be obvious to a person of ordinary skill in the art to employ the acrylic acid-containing copolymers taught by Huang, with higher content of acrylic acid, in the process taught by either Nishiguchi et al. (US 6,046,040), Nishiguchi et al. (JP 2001-220399 A) or Yamada et al. (Carbohydrate Research 305 (1998) as a primer carrier for a glycosylation reaction at elevated temperature so that the polymer is soluble in the reaction temperature (which results in increased product yield) and is insoluble when the temperature is increased (which facilitates product isolation).

***Conclusion***

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Contact Information***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vu Nguyen whose telephone number is (571)270-5454. The examiner can normally be reached on M-F 7:30-5:00 (Alternating Friday Off).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Wu can be reached on 571-272-1114. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vu Nguyen  
Examiner  
Art Unit 1796

/David Wu/

Supervisory Patent Examiner, Art Unit 1796